Innate immunity (Metchnikoff, 1908):
- direct response to pathogens
- conserved microbial products
- not "antigen-specific"

Adaptive immunity (Ehrlich, 1908):
- specific antibodies
- variable antigens
- stimulation of T- and B-cells

T cell stimulation requires "antigen presentation" by antigen presenting cells
T-lymphocytes recognize antigen fragments directly: help B cells, kill targets

T-cell antigen receptor = TCR

Diversity generator: TCR gene rearrangement

CD8 T cell

CD4 T cell

Don Wiley et al
Antigen processing pathways inside the cell

Antigen presentation for amateurs & professionals

MHC class I:
Expressed by all nucleated cells

MHC class II:
Expressed by specialized cells:
- B-cells, macrophages,
  dendritic cells

Why are dendritic cells special?
- Most efficient of all APCs
- Carry antigen from tissues to LN’s
- Initiate all antigen specific T cell responses
- Maintain 'tolerance' to self antigens
- Activated in response to (innate) microbial signals
Innate immunity (Metchnikoff, 1908):
- direct cellular response to pathogens
- detects shared microbial ‘patterns’
- not ‘antigen-specific’

Connected via DCs

Adaptive immunity (Ehrlich, 1908):
- specific antibodies
- variable antigens
- stimulation of T- and B-lymphocytes

Adapted via DCs (Steinman, 2007):

immature

mature + immature
The American Society for Cell Biology 5

Membrane traffic during DC maturation

Mechanisms of pH regulation in DC lysosomes/phagosomes

low MHC, costimulators efficient endocytosis antigen accumulation

high MHC, cytokines high costimulators (CD86) antigen presentation

Regulation of acidification activates antigen proteolysis

Lysosomal pH of immature DCs: pH 5.5  
Lysosomal pH of mature DCs: pH 4.5  
PpH optimum for lysosomal proteases: <pH 5

Stepwise processing of the MHC class II-li chain complex

Endosomes

Plasma membrane

HLA-DM  
Low pH

cystatin C

Lysosomal targeting

Goat complex

Mature DCs

Immature DCs

αβ-CLIP

αβ-CLIP

αβ-p10

αβ-p10

αβ-chain

αβ-chain
Stimulated DCs transport MHC class II from lysosomes

- LPS

Tubules can migrate to the cell periphery

- LPS
MHC class II molecules escape from lysosomes to the DC surface by "retrograde" transport.

The Classical View of what goes on inside of Lysosome
MHC class II molecules are selectively retained at the surface during maturation: why?

Down regulation of endocytosis upon maturation

MHC class II is often on internal vesicles in MVBs/lysosomes of immature DCs.

Ubiquitin: covalent attachment to lysine residues by E3 ligases.

MHC class II β chain has a conserved cytoplasmic domain lysine.

Human ——— HLA-DR

Mouse ——— H-2 IA

H-2 IE

<table>
<thead>
<tr>
<th>Lumen</th>
<th>Cytosol</th>
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<tbody>
<tr>
<td>Human</td>
<td>FIIXVKRSMAFRRGPL –c'</td>
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<tr>
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<td>RNDYGSGLQFGFLS –c'</td>
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</tbody>
</table>
Regulated ubiquitination of MHC class II allows selective retention at surface in mature DCs

Why are dendritic cells special?

- MHC class II: CD4 T cell response
- MHC class I: CD8 cytotoxic T cell response

Shin et al. (2006) Nature

MHC class II is not ubiquitinated in mature DCs
Antigen processing pathways inside the cell:

- Golgi complex
- Endoplasmic reticulum (ER)
- Endosomes
- Lysosomes
- Plasma membrane

Antigen processing pathways:
- Transport of antigens to ER
- Protein synthesis in ER
- Enzymatic processing in endosomes
- Delivery of class I or class II complexes to the cell surface

Cross presentation of exogenous antigens on MHC class I:

- Endosomes
- Proteasome
- MHC II pathway
- MHC I pathway
- ER
- TAP1/TAP2
- Peptide loading

Cross presentation allows DCs to present viral antigens without actually being infected!
How does DC cell biology control the immune response?

How does DC cell biology control the immune response?

**Innate immunity**
- direct cellular response to pathogens
- detects shared microbial ‘patterns’
- not ‘antigen-specific’

**Dendritic cell maturation**

**Adaptive immunity**
- specific antibodies
- variable antigens
- stimulation of T- and B-lymphocytes

**Toll-like receptors** as ‘bar code’ readers

**Innate immunity**
- direct cellular response to pathogens
- detects shared microbial ‘patterns’
- not ‘antigen-specific’
12 different Toll-like receptors (TLRs) serve as the innate immune system’s “sensor.”

TLRs on DCs as “bar code reader”

DC cytokines stimulate, and instruct T cells where to go and what to do
DC cytokines stimulate and instruct T cells where to go and what to do

- Th1 T cell
- T cell
- Dendritic cell
- IL-12

CD8 killer T cells
CD4 T helper type 1
CD4 T helper type 2
Inflammatory Th2
CD4 T helper type 17
Central memory T cells
Effector memory T cells
Multi-cytokine T cells
Regulatory T cells

In the thymus: self-reactive T cells are "deleted"...but some escape
DCs that mature without microbial stimulus do not release cytokines & induce T regs

No infection
- Immature
- Tolerogenic

Infection
- Immature
- Immunogenic

Too little tolerance:
- Autoimmunity: autoimmune diabetes, lupus
- Chronic inflammation: arthritis, Crohn's disease, ulcerative colitis, MS?, asthma

Too much tolerance:
- Cancer?
- Chronic viral infections: CMV, HIV-AIDS?